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Topical Review

Neurobiology of Continuous Spike-Wave in Slow-Wave Sleep and Landau-Kleffner Syndromes

Naoum P. Issa MD, PhD *

Department of Neurology, The University of Chicago Medical Center, Chicago, Illinois

ABSTRACT

BACKGROUND: Several pediatric seizure disorders have common electrophysiological features during slow-wave sleep that produce different syndromes based on which part of the developing brain is involved. These disorders, of which continuous spike-wave in slow-wave sleep and Landau-Kleffner are the most common, are characterized by continuous spike-wave activity during slow-wave sleep, developmentally regulated onset and termination of abnormal electrical activity, and loss of previously acquired skills. Over the last 20 years, a variety of basic science findings suggest how spike-wave activity during sleep can cause the observed clinical outcomes. **METHODS:** Literature review and analysis. **RESULTS:** The role of slow-wave sleep in normal cortical plasticity during developmental critical periods, how disruption of slow-wave sleep by electrographic seizures could affect cortical maps and development, and the organization and functional connectivity of the thalamic structures that when damaged are thought to produce these seizure disorders are reviewed. **CONCLUSIONS:** Potential therapeutic directions are proposed based on the mechanisms of plasticity and anatomical structures involved in cortical plasticity during slow-wave sleep.

Keywords: CSWS, continuous spike-wave during slow-wave sleep, Landau-Kleffner syndrome, electrical status epilepticus during sleep, ESES, critical period, ocular dominance plasticity

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Introduction

Continuous spike-wave in slow-wave sleep (CSWS) and closely related Landau-Kleffner syndrome (LKS) are two disorders in a class of epilepsies that affect school-aged children, causing loss of previously acquired function and degradation of cognition.[1] Often misdiagnosed as one of the autism spectrum disorders, the prevalence of these "encephalopathy related to status epilepticus during slow sleep" (ESES) epilepsies is likely underestimated, but currently, they are thought to represent only about 1% of childhood epilepsies (reviewed by Hughes).[2] Although there has been good effort to broaden the possible therapies for these rare disorders, their pathophysiology is still incompletely understood.

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* Communications should be addressed to: Dr. Issa; Department of Neurology; The University of Chicago Medical Center; 5841 South Maryland Avenue, MC 2030; Chicago, Illinois 60637-1470.
E-mail address: naoumpissa@gmail.com.

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The common features of ESES include nearly continuous spike-and-wave electrical patterns during non-rapid eye movement (REM) sleep, onset of symptoms in the first few years of life, clinical seizures (although not all children have seizures in spite of having spike-and-wave activity), resolution of abnormal electrical activity (and seizures) in teenage years, and loss of already acquired abilities without recovery of these abilities after abnormal electrical activity and clinical seizures terminate. These commonalities argue for a shared disease mechanism that manifests as different disorders when different thalamocortical circuits are involved. Landau-Kleffner, for example, is characterized by spike-and-wave during non-REM sleep in the auditory cortical areas so it presents as acquired auditory agnosia.[3] CSWS typically affects frontal areas so more often presents with difficult-to-manage clinical seizures and more global behavioral and cognitive deficits.[4]

These disorders seem strongly linked to developmental critical periods for a variety of reasons (some of these links have been previously reviewed).[5,6] First, the disorders start and end at nearly the same time that critical periods start

and end. Second, electrical status epilepticus during sleep would be expected to drive maladaptive plasticity during the critical period, and the termination of the critical period would cement those maladaptive changes, possibly explaining the long-lasting effects of ESES on cortical function. Finally, non-REM sleep is known to be important in critical period plasticity (to a different degree than sleep affects adult learning), and therefore could explain why sleep disruption does not just prevent new learning but would actually degrade previously developed cortical structures. Several recent reports have synthesized the current work on the pathophysiology and treatment modalities of ESES.[7-10] In this review, the pathologic effects of these disorders are discussed in the context of the role that sleep plays in critical period plasticity.

Visual critical period as the model system

The notion of a critical period for cortical development grew out of the electrophysiological studies of Hubel and Wiesel in the cat primary visual cortex.[11-14] Their initial studies revealed that alternating neuronal columns within primary visual cortex react preferentially to either ipsilateral or contralateral eye stimulation. Deprivation of vision through one eye during the early postnatal period results in a shift in the balance of ipsilateral and contralateral drive, with an expansion of cortical territory driven by the nondeprived eye and shrinkage of the territory driven by the deprived eye. As the animal aged, the amount of shift with monocular deprivation decreased. They called this developmental labile time window the "critical period," and the concept has persisted, sometimes with different names such as the "sensitive period." Although critical period plasticity is no longer thought to underlie the gross organizational development of cortex,[15-17] it does allow cortex to adapt to the idiosyncrasies of individuals and their environment.

Critical period plasticity is distinct from learning that happens in the mature individual. The most profound difference is in the anatomic changes that underlie the different types of plasticity. In critical period plasticity, the responses of all cortical laminae change, with a rearrangement of thalamic inputs to cortical layer 4 that propagates through supragranular and infragranular layers.[18,19] After the end of the critical period, however, plasticity is much more limited, with no apparent shift in the thalamocortical inputs.[20] As a result, early plasticity can fundamentally restructure a cortical area from input to output, although adult plasticity can only change upstream circuitry that then modulates a relatively fixed set of inputs.

The practical implication is that the cerebral cortex adapts to the environment of the child much more profoundly than it does to the environment of the adult. The structure of the brain at the end of the critical period is, for all intents and purposes, "locked in" for the remainder of the child's life. Although this would be beneficial for adaptation to developmental abnormalities that are irreversible like monocular blindness or a missing limb, it prevents recovery when cortex is locked into an abnormal state even if the driving stimulus normalizes after the end of the critical period. Such is the case with ESES, the organization of cortex is driven into an abnormal structure by state-dependent (sleep) epileptiform activity during the critical period, but the abnormal electrical activity stops once the critical period is over. Because the thalamocortical inputs to cortex are no longer plastic once the abnormal electrical activity stops, limited functional recovery is possible.

Timing of critical periods

Cortical areas develop with different time courses; so it is not surprising that each cortical area or cortical function seems to have a slightly different critical period. Even for vision, the best-studied modality for understanding critical periods, there appear to be multiple critical periods in the human. For example, the critical period for acuity loss driven by visual deprivation seems to be over by age 10 years,[21] whereas the susceptibility period for stereopsis concludes around age 6 years.[22] In the context of ESES, however, visual critical periods are not meaningful because vision is rarely affected (likely because there is no dominant hemisphere for vision, and at worst ESES in primary visual cortex would cause hemifield blindness).

The critical period for language, however, is of utmost importance because it defines the therapeutic window during which treatment might minimize aphasia in LKS. Although the exact age range that covers the language critical period is often debated (for example refer the studies by Johnson and Newport,[23] Birdsong and Molis,[24] and Nicholas and Geers),[25] the ages at which Landau-Kleffner patients have electrographic seizures fall within the commonly agreed on critical period. Figure 1

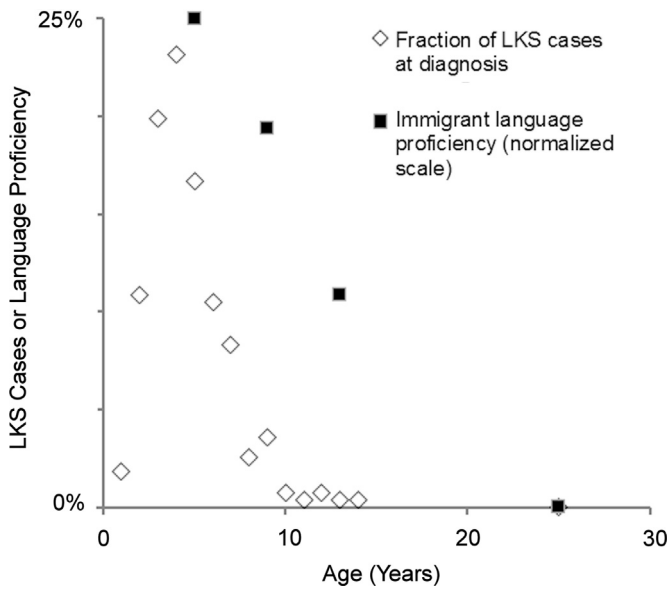

FIGURE 1.
LKS age of onset and language critical period. Data for language acquisition replotted on an arbitrary scale from the study by Johnson and Newport[23] (squares). Acquisition of English as a second language was tested in adults who had immigrated to the United States at different ages. The original proficiency data ranged from 269.3, the best average performance on the language test which was attained by those who immigrated at the youngest ages, to 210, which was the average performance by the group with the oldest age at immigration; the average score of native speakers was 268. The distribution of LKS cases by age at diagnosis is replotted from the data obtained from the study of Stefanatos[26] (diamonds). LKS, Landau-Kleffner syndrome

depicts the rough envelope of the critical period for language development, determined by measuring adult English language proficiency as a function of age of immigration to the United States,[23] along with the distribution of ages at which LKS has been diagnosed.[26] All the reported cases of LKS occur within the language critical period window, and most cases are diagnosed at the peak language development ages (aged less than 7 years). The age distribution at which electrographic seizures stop has not been reported with the same accuracy as the onset age, but the typical progression of the disease results in seizure termination in the teenage years. Importantly, the older the child at the onset of the disease, the better the outcome,[27] consistent with weaker plasticity toward the end of the critical period.[20] It is not clear whether the neuronal or molecular changes that terminate the critical period also terminate electrographic seizure activity, or whether seizures stop for some other unrelated reason. Regardless, the electrographic seizures are perfectly timed to disrupt cortical activity during its most sensitive period and to stop when they would no longer do permanent damage.

Understanding the effects of ESES on cortical organization promises a better understanding of normal cortical development. In LKS, language function is lost in spite of the ability of the brain, in theory, to switch hemispheric dominance or redistribute functions across different cortical areas at an early age. In other pediatric disorders there have been strong of shifts in language area from left hemisphere to right in individual patients. Villarejo-Ortega et al.,[28] for example, claim there was transfer from left to right hemisphere in a 6-year-old patient with Rasmussen encephalitis. Similarly, Gallagher et al.[29,30] found that in patients with seizures and tuberous sclerosis, the burden of tubers in language areas was inversely correlated with left-hemisphere language processing: the more tubers a patient had, the more likely they were to have language functions distributed across both hemispheres rather than just the left. This argues that abnormal electrical activity by itself—even in classic language areas—should not cause a loss of language, but that something about the circuits activated by ESES (perhaps through an effect on dendritic pruning) prevent redistribution of function to other cortical areas.

The role of sleep in critical period plasticity

It might initially be surprising that abnormal nighttime electrical activity has such devastating effects on processes that are learned and used during wakefulness. However, a growing body of research reveals that sleep is an important component of learning. Studies in adults reveal that sleep deprivation inhibits consolidation of memories.[31] In a small study that included two children with ESES, Urbain et al.[32] asked whether interictal activity inhibits memory consolidation in a similar way as sleep deprivation does in adults. They tested whether children with abnormal nighttime electrical activity improved in their ability to recall a pair of words to the same extent that normal age-matched controls do, and found that recall of children with ESES was degraded after sleep rather than improved. In one patient in whom steroid treatment was successful in stopping the abnormal nighttime electrical activity, sleep-dependent memory consolidation returned. This was the first direct demonstration that ESES affects learning and in particular language-dependent learning.

The type of learning studied by Urbain et al., i.e. declarative learning, is important for day-to-day acquisition of new vocabulary; however, vocabulary is the type of material that can still be acquired as an adult. The language deficits that develop with LKS go beyond loss of vocabulary and represent problems with the fundamental processes of phonological auditory discrimination.[33] Just as amblyopia results from early visual deprivation through reorganization of the primary visual cortex during the critical period, so are the auditory abnormalities of LKS likely due to fundamental reorganization of cortical structure during the auditory or language critical periods. If ESES is to blame for this reorganization, then sleep must play a much more profound role during developmental critical periods than just degrading declarative memory consolidation.

As the previous section reveals, the physical structures and functional maps within cortex rearrange during the critical period to adapt to an individual's unique sensory inputs. Frank and colleagues asked whether sleep is important to the normal progression of critical period plasticity. They addressed this question in critical period cats monocularly deprived of vision for brief periods.[34] Cats at 4- to 5- weeks of age are at the peak of their visual critical period (Fig 2). Six hours of monocular deprivation produces a shift in the amount of cortex dominated by each eye: about half of the cortex normally encodes input from each eye, but after 6 hours with one eye closed, there is a shift such that the open eye takes over more cortex and the closed eye loses cortical territory. After 6 hours of monocular deprivation and another 6 hours of sleep in the dark, the amount of shift in favor of the open eye doubles, although there is no additional visual stimulus. There is both a shift in the sensitivity of individual neurons in visual cortex and in how inputs are mapped onto the cortical architecture. If cats are instead sleep deprived in the dark for 6 hours after the initial monocular deprivation period, the shift is less than that with six hours of monocular deprivation alone. These results suggest that during the critical period, sleep plays an important role in the development of normal cortical architecture and function.

An initially surprising result of Frank et al.[34] was that the amount of plasticity during sleep varied linearly with the amount of non-REM sleep an individual cat had. Figure 3 summarizes the findings, in which animals that had nearly zero non-REM episodes during the 6 hours after monocular deprivation had almost no shift in ocular dominance columns, whereas those with a large amount of non-REM sleep had changes in cortical organization equivalent to an animal that had double the exposure to monocular stimuli. Normal cortical activity during non-REM sleep is therefore fundamentally important for critical period plasticity, without it the neural circuitry within cortex does not change effectively in response to the environment.

Two studies argue that the effect of slow-wave sleep on learning is a local phenomenon, occurring selectivity within

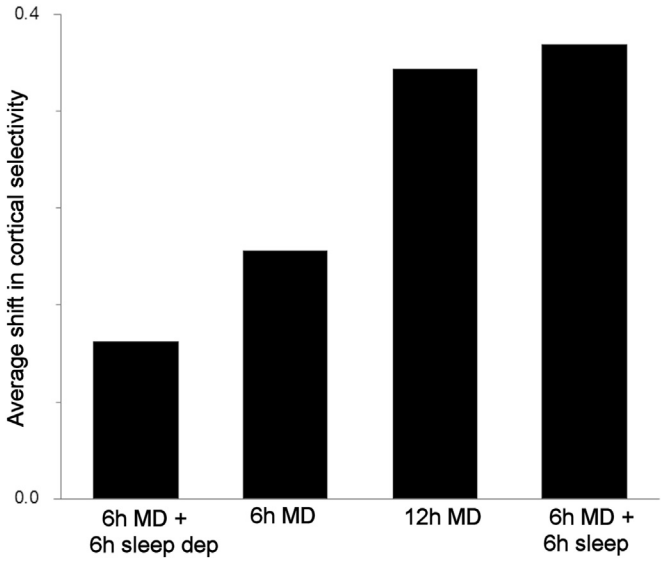

FIGURE 2.
Sleep potentiates cortical ocular dominance plasticity and sleep deprivation prevents its progression. In the normal developing cat, 6 hours of visual deprivation through one eye causes the number of neurons in the primary visual cortex to shift to be dominated by the nondeprived eye. The "6h MD" condition reveals the normal amount of shift in cortical selectivity after 6 hours of monocular deprivation (measured as "Shift Index," which is defined in the study by Frank et al.).[34] The "12h MD" condition reveals the amount of shift in cortical selectivity after 12 hours of monocular deprivation; the additional 6 hours of visual deprivation produces approximately 40% more shift than 6 hours alone. When animals were allowed to sleep ad lib in the dark for 6 hours after the initial 6-hour monocular deprivation period (the "6h MD + 6h sleep" condition) cortical plasticity proceeded to the same degree as although the animal had received an additional 6 hours of visual stimulation. However, when cats were kept awake in the dark for the 6 hours after the initial monocular deprivation period (the "6h MD + 6h sleep dep" condition), there was a significantly less shift in neuronal selectivity compared with 6 hours of monocular deprivation alone. Data replotted from the study by Frank et al.[34] dep, deprivation; h, hour; MD, monocular deprivation

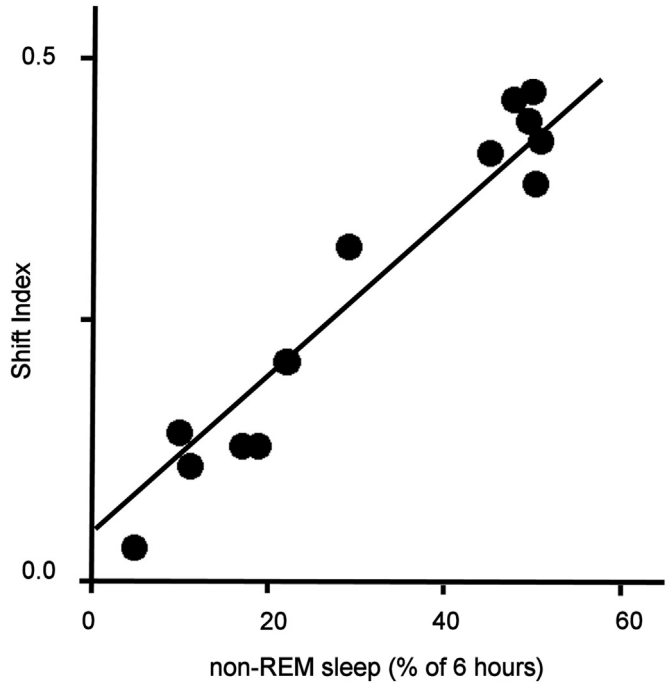

FIGURE 3.
Cortical plasticity proceeds during non-REM sleep. Frank et al. measured the amount of cortical plasticity (represented by the Shift Index, as depicted in Fig 2) produced as a function of the amount of non-REM sleep the animal got in the 6 hours after a period of monocular deprivation. Each circle represents data from an individual cat. Although the amount of REM sleep was negatively correlated with the degree of cortical plasticity (not illustrated), the amount of cortical plasticity was a positively and linearly correlated to the amount of non-REM sleep animals got after a period of monocular deprivation. Data replotted from the study by Frank et al.[34]

the small regions of cortex that are stimulated during training. Huber et al.[35] described that increases in delta-range power during slow-wave sleep correlate with the degree of learning in an implicit-memory motor task in adult humans. Importantly, the increase in delta-range power that correlates with learning is spatially local (evident only in a consistent part of parietal cortex) and temporally local (only evident on the night after the learning task and not a week before or after). In the developing visual cortex and/or non-REM sleep model system first used by Frank et al.,[34] Jha et al. described that focally inhibiting activity in primary visual cortex during non-REM sleep with lidocaine prevents cortical plasticity.[36] Together, these studies[35,36] implicate local slow-wave activity in cortical plasticity and suggest that disruption of slow-wave activity in a small area of cortex can prevent normal cortical development during the critical period.

One indication that a similar process is at play in ESES patients comes from a study of how slow waves change over the course of a night. Based on the finding of learning-associated local changes in slow-wave activity,[35] Tassinari and Rubboli proposed that focal disruption of slow-wave sleep could underlie degradation of cognitive function in ESES patients by preventing synaptic downscaling.[6] In an attempt to validate this hypothesis, Bolsterli et al. asked if there is a difference between ESES patients and normal age-matched controls in how slow waves change over the course of a night.[37] The slope of slow waves has been associated with synaptic synchrony,[38] and so Bolsterli et al. used it as a marker for synaptic strength. They found that while the slope of slow waves decreases between the first and the last hour of sleep in normal controls, the change in slope is inconsistent across patients with ESES, arguing that the synaptic downscaling thought to occur with normal slow-wave sleep is impaired with ESES.

Although the findings of Bolsterli et al.[37] provide support for the hypothesis of Tassinari and Rubboli,[6] there are caveats. First, the slope of slow waves is an indirect measure of synaptic strength, without direct validation in humans. This is compounded by the difficulty of automated slope detection in abnormal electroencephalographs (EEGs) (Bolsterli et al. go to great lengths to minimize errors in automatic detection and explain the potential impact, but it cannot be completely avoided).[37] More importantly, as Vyazovsky et al.[38] point out, it is not clear what the expected change is in synaptic strength for normal critical period development. Regardless of these caveats, the findings of Bolsterli et al. rather convincingly demonstrate that slow-wave activity, not just spike-wave activity, is abnormal in patients with ESES.[37]

Given the role of non-REM sleep in critical period plasticity, the continuous spike-and-wave activity in slow-wave sleep of epileptic encephalopathies seems unfortunately optimized to disrupt the process of activity-dependent cortical maturation. In LKS, disruption in the auditory areas of cortex appears to prevent the normal development of circuits important in phoneme recognition leading to auditory agnosia. With CSWS in frontal areas, the disrupted maturation of circuitry important for behavioral control leads to neuropsychologic deterioration. Rare reports of continuous spike-wave during sleep in occipital cortex suggest it can disrupt the development of the visual system, resulting in visual agnosia.[39] Although the location of the abnormal EEG activity is important for prognosis, the underlying mechanism in which abnormal cortical activity during non-REM sleep disrupts the development of normal cortical architecture seems independent of the precise cortical area involved.

Degradation after initial development

One defining characteristic of this class of epilepsy is the loss of function after its initial acquisition. Although this might seem counterintuitive given the vast adaptive potential of the young brain, there is an analog in the neurodevelopmental literature. Crair et al.[40] looked at the development of cortical functional architecture in the absence of normal sensory inputs. Using the cat visual cortex as a model, they mapped functional responses in animals of different ages that never had visual experience. They found that even in the absence of vision, the organization of orientation preference in the visual cortex initially develops normally. After this initial normal development, however, cortical orientation selectivity begins to degrade with prolonged visual deprivation. Cats that instead were allowed to have normal eye opening and visual experience had a strengthening of cortical orientation selectivity and continued to have normal visual development. This suggests that maintained normal sensory inputs are important to the development of normal cortical architecture and the resulting function.

With ESES, the situation is, very likely, worse than simply a lack of normal sensory inputs. The electrical spike-and-waves during sleep provide an abnormal pattern of activity that can potentially engage the normal plasticity mechanisms of the critical period brain. If all sensory cortical areas are like the visual cortex, there is both local variation in neuronal sensitivities and long-range horizontal connections among clusters of neurons with similar sensitivities (the structure of maps in visual cortex was reviewed by Issa et al.).[41] The development of these long-range connections, and to some extent the local variations in sensitivities, is dependent on the correlations in normal neural activity driven by correlations in the sensory environment. Without sensory inputs, as in the experimental protocol of Crair et al.,[40] these normal correlations are absent. With continuous spike-and-wave activity, however, new nonfunctional correlations in neural activity are present, and the cortical architecture that develops is not well adapted to the actual sensory environment present during wakefulness.

The sleep deprivation studies of Frank et al.[34] also suggest that abnormal electrical activity during sleep can cause loss of appropriate adaptive changes during the critical period. As mentioned in the previous section, and depicted in Fig 2, cats that were sleep deprived in the dark after the monocular deprivation period revealed a decrease in the amount of cortical shift than which occurs during 6 hours of monocular deprivation. This argues that when cortical activity is not allowed to proceed normally during sleep (and non-REM sleep in particular) there can be degradation of previously acquired cortical adaptations.

A potential role for thalamus in ESES

Identifying the origin of the spike-and-wave discharges in ESES is central to developing treatments. Most studies, until recently, have focused on the potential role of cortical circuits and activity in the genesis of spike-wave activity during sleep. For example, a retrospective analysis of 117 cases found polymicrogyria to be the most common anatomic abnormality in children with ESES (note that this study used a definition of ESES that excluded Landau-Kleffner and included benign childhood epilepsy with centrotemporal spikes and Panayiotopoulos syndrome).[42] The growing understanding of the thalamocortical circuitry in regulating information flow and states of alertness, however, suggests the search for a source should include the thalamus.

A growing body of evidence implicates damage to the thalamus as a potential factor in ESES. Monteiro et al.[43]and Guzzetta et al.[44] proposed that damage to the thalamus could be the reason continuous spike-wave activity occurs during sleep. Both groups observed the similarity between the electrical activity that developed in their patients and that found in experimental animals lacking a thalamus on one side. Steriade and Contreras[45] found that animals in which a unilateral thalamectomy was performed developed continuous spike-wave activity that lasted for minutes at a time. The animals were anesthetized with pentobarbital, and although their EEG pattern was described as “sleep-like,” it is difficult to know whether the spike-wave activity would manifest in natural sleep and whether it would appear specifically during non-REM sleep. Nonetheless, the similarity in electrophysiological patterns between the experimental systems and those observed in patients with ESES suggests that thalamic damage might underlie continuous spike-waves during sleep.

Clinical evidence for the role of thalamic injury in ESES

Monteiro et al.[43] suggested that thalamic injury could be related to ESES after following a child who suffered a primary neonatal thalamic hemorrhage and subsequently developed ESES. Guzzetta et al.[44] looked at a series of 32 children admitted with thalamic injuries and found that all but three had some sort of electrographic or clinical seizure. All 29 with seizures revealed abnormal activity patterns in slow-wave sleep, with 12 meeting the full criteria for ESES. Kersbergen et al.[46] studied children with a history of neonatal thalamic hemorrhage associated with straight sinus thrombosis and found a high risk of developing ESES-spectrum disorders even in the absence of cortical damage.

Fernandez et al.[47] asked the converse question: were children with ESES more likely to have thalamic injuries? They examined brain abnormalities of 100 children with prominent sleep-potentiated epileptiform activity. They split this group into children whose nighttime EEG met the criteria for ESES (21 of the 100 children had >85% of non-REM time occupied by epileptiform discharges) and those that did not meet the criteria (79 of 100 children had discharges occupying 50-85% of their non-REM sleep; "non-ESES"). The children with ESES were five times more likely to have thalamic lesions than children who did not meet the diagnostic criteria for ESES. In spite of the small number of patients (in fact, given how rare the ESES disorders are, these are large series), the connection between thalamic injury and abnormalities in slow-wave sleep seems convincing.

Further support for the role of thalamic injury in ESES comes from a small number of surgical interventions and functional neuroimaging studies. Separating hemispheres with damaged thalamocortical circuits from the normal contralateral hemisphere has eliminated generalized CSWS in two cases. Battaglia et al.[48] described two individuals with CSWS who improved after functional hemispherectomy and transection of the corpus callosum. The surgical interventions resulted in the cessation of generalized CSWS, with no subsequent epileptiform activity on EEG in one individual and only focal spikes observed in the other. There was also clinical improvement in cognitive, motor, and social development in the children. Because abnormal cortex was resected in both procedures, these cases do not by themselves prove a connection between thalamic injury and CSWS. Added support, however, comes from functional brain imaging studies that suggest there is activation of a stereotypical circuit consisting of perisylvian cortex and thalamus (with decreased activity in caudate nucleus) during continuous spike-and-wave activity during slow-wave sleep.[49] Together with the association between thalamic lesions and ESES, these data argue strongly that disruption of unilateral thalamocortical circuits can lead to ESES.

The physiology of thalamus in relaying information

The thalamus plays a central role in regulating cortical activity by determining when and how much information gets relayed to the cerebral cortex and as such is in a position to disrupt cortical activity if it is damaged. Thalamic relay neurons are thought to function in two modes, a tonic mode and a burst mode, and each of these modes predominates either in wakefulness (or attention) or sleep (or inattention).[50,51] In the tonic mode, which predominates during attentive states, thalamic relay neurons modulate their firing rate reasonably faithfully based on the input they receive. The firing rate of neurons in the lateral geniculate nucleus (LGN), for example, modulates sinusoidally with the intensity of a grating drifting in front of the eye.[50,51] When in burst mode, on the other hand, the relay neuron is generally silent unless a very strong stimulus is presented; in the visual system, for example, this could be a large change in image brightness. The burst mode predominates during sleep or inattention and the relay neuron would, after a period of quiescence, fire a rapid short burst of action potentials in response to a sudden intense stimulus to "wake up" its cortical target. Although information is transmitted to the cortex by this burst of activity, the information is not a faithful representation of a real-world stimulus.[52]

The duality of tonic and burst modes is thought to be important in the learning that occurs during sleep. As discussed in the previous section, in the sleep state, the cortex is isolated from the sensory environment allowing it to consolidate salient activity patterns that were introduced during wakefulness through cortical replay.[53] A normally functioning burst mode is required for this isolation because relay neurons are hyperpolarized when in burst mode, preventing random (or stimulus-driven) fluctuations in the activity of input neurons from being sent on to cortex and disrupting replay. However, one can speculate that damage to the thalamus, either to thalamic relay nuclei or the thalamic reticular nucleus (TRN), could cause repeated rhythmic firing that disrupts cortical replay with meaningless bursts.

The TRN as possible locus of pathology

Left unanswered is why, in the absence of normal thalamic activity, the cortex would become epileptogenic. In the case series of Guzzetta et al.,[44] the vast majority of patients had damage to the TRN (91% of patients had damage to the TRN, compared with 87% that had damage to the ventral nuclear mass, 66% had damage to the lateral posterior nuclear mass, and 37% had damage to the medial nuclear mass; recall that the patient series was selected for having thalamic injury). Based on this, they proposed that damage to the TRN might the primary etiology of ESES.

The TRN has several characteristics that make it a good candidate for the locus for ESES pathology. The TRN acts as a feedback control center between the cortex and thalamus.[52] Thalamic relay neurons are in burst mode when they are hyperpolarized for at least 100 ms. A powerful stimulus that induces bursting in the thalamus is relayed to the cortex which in turn should, through cortico-thalamic feedback, cause the thalamus to transition into tonic mode and "wake" that thalamocortical circuit. During normal slow-wave sleep, thalamic neurons are held hyperpolarized by the activity of the TRN, which forms a shell of inhibitory neurons along the ventral thalamus. In ESES, however, the putative thalamocortical bursts that are proposed to underlie spike-wave cortical activity do not seem to push the circuit out of burst mode and into tonic firing mode. Guzzetta et al.[44] suggested that damage to the TRN produces an imbalance in γ-aminobutyric acid (GABA)—mediated tone within the thalamus, but the exact defect needed to allow repetitive spiking without transition to the tonic mode solely during slow-wave sleep has not yet been definitively demonstrated.

The role of TRN and the connections between thalamus and cortex in generating spike-wave activity is supported by studies on the origin of absence seizures. There are many theoretical models for the generation of absence seizures, most of which invoke thalamocortical circuits in either generating or perpetuating spike-wave activity (several models are reviewed by Meeren et al.).[54] Buzsaki[55] in particular invoked the TRN as a pacemaker for spike-wave discharges. Whether spike-wave generation in ESES is the

same as in the absence seizures is unclear. For example, in the Genetic Absence Epilepsy Rats from Strasbourg (GAERS) rat model of absence seizures, selective ablation of the TRN abolishes spike-wave discharges,[56] although the opposite is expected in CSWS because TRN lesions seem to produce spike-wave activity during sleep. Regardless, the TRN and other thalamocortical circuits are implicated in spike-wave activity in both absence and ESES seizure disorders.

There is also a clear spatial connectivity pattern between the TRN and relay nuclei of the thalamus that could explain how the various ESES syndromes could affect restricted sensory or motor modalities. In the mapping experiment of Llano et al.[57] shown in Fig 4, for example, regions of about 100 microns in the ventral posteromedial nucleus of the somatosensory system are connected to similarly sized regions within the TRN. This means that damage to a small region of a relay nucleus, or alternatively to TRN, could result not in generalized dysfunction of the thalamus, but rather in localized dysfunction during sleep of the circuit mediated by the relay nucleus. Damage to the TRN adjacent to the medial geniculate nucleus (or higher order relay nuclei of the auditory system), for example, could cause disruption in sleep states just within the auditory system, potentially causing the symptoms of LKS. This hypothesis is directly testable in animal models.

Developmental circuits and receptor expression

The time-locked onset and resolution of ESES suggests that normal developmental changes might trigger or eventually suppress electrographic seizure activity. Several authors have nicely reviewed many of the normal developmental processes in cortex and how they correlate with epileptogenesis during the critical period.[9,58,59] Among the most likely factors that could determine epileptogenicity is the developmentally regulated expression of excitatory and inhibitory receptor ion channels in the neocortex. Excitatory glutamatergic ion channels, including N-methyl-D-aspartate receptor (NMDA) channels needed for long-term potentiation, reach maximal expression in neocortex near the peak of the critical period. Inhibitory channel expression increases during the critical period and is important to initiating critical period plasticity by suppressing spontaneous activity and allowing stimulus-driven cortical activity to shape cortical connections.[60] This suggests that the increase in cortical inhibition might, counterintuitively, permit the onset of ESES. Equally important, these channels appear to mediate to sleep-dependent plasticity;[61] so their regulation is central to the functions disrupted by ESES.

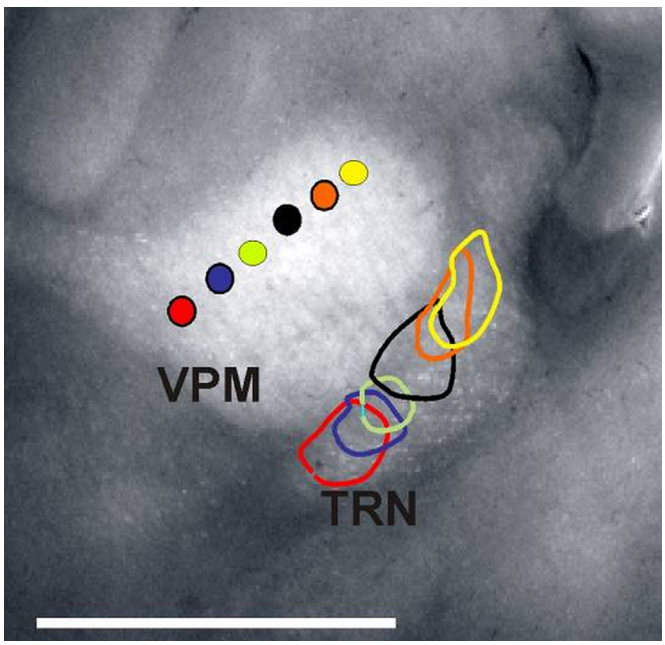

FIGURE 4.
Point-to-point connections between a thalamic relay nucleus and the thalamic reticular nucleus (TRN). Llano et al.[57] used a combination of photo-uncaging of glutamate and flavoprotein autofluorescence imaging to optically map the connections between ventral posteromedial nucleus (VPM) and TRN in slices of mouse thalamus. Glutamate was uncaged at the points plotted in the VPM, and flavoprotein autofluorescence (a measure of postsynaptic neuronal activity) was recorded in the corresponding regions outlined in the TRN. Adapted with permission from Llano et al.[57]

The epileptogenic role of developmental changes in other parts of the thalamocortical circuits is less clear. For example, little is known about whether damage to the subplate could lead to ESES. The subplate is a transient population of neurons underlying cortex during development and is important for the normal maturation of cortical organization.[62] Because of its location and susceptibility to early developmental injuries,[63] damage to the subplate could affect aspects of thalamocortical development that predispose to ESES. This is a particularly difficulty topic to study, however, as much of the subplate has regressed by the time ESES is clinically evident.

The functional development of the thalamus is less well described than cortical development. Although classic experiments reveal that early activity in the periphery, for example in the retina, helps organize thalamic relay nuclei,[64,65] the temporal expression pattern of ion channels within different thalamic compartments is not well described. Increased expression of T-type calcium channels in thalamus has been evident in animal models of absence epilepsy, and the onset of ESES might analogously be related to a developmental increase in T-type channel expression when in the context of previous thalamic injury. The normal developmental expression of T-type channels is not known, and it would be interesting to learn if expression increases in parallel with the time course of electrographic seizure onset.

Potential therapeutic implications

Reinstating post-critical period plasticity after abnormal EEG activity ends

Significant effort is going into developing therapeutic approaches to reinstate cortical plasticity in adults specifically to permit functional recovery after a stroke. In the case of stroke, the function of ischemic areas has been lost because the tissue is dead. Other cortical areas would therefore have to be recruited to pick up the lost functions, which would require the new area to give up some of its native function and rewire to receive new thalamic inputs. The therapeutic requirements for the epileptic encephalopathies are less extreme. In this disease class, the

cortical tissue is still viable and the thalamic inputs appear to be generally intact but are likely abnormally organized. If critical period–like plasticity could be reinstated in young adults whose abnormal EEG activity has stopped, it may be possible that activity-dependent plasticity driven by normal sensory input could lead to reacquisition of normal function.

A recent report in normal adult men suggests that valproic acid might give limited access to critical period–like plasticity.[66] Work in mice reveals that inhibition of histone deacetylase (and the resulting reopening of chromatin structure to presumably allow transcription) can increase cortical plasticity after the critical period has ended.[67] Because valproic acid inhibits histone deacetylase, among other actions, Gervain et al.[66] hypothesized that treatment in adult humans might allow increased plasticity. In a small double-blinded trial they gave volunteers either valproic acid or placebo and tested how well they learned to identify absolute pitch with training, a skill that typically develops only in children who start musical training before the age of 6 years. The group that received valproic acid learned to identify absolute pitch better than those that received placebo. Although the direct implications of this very small "proof of concept" study are limited, it suggests a rationale for studies on the duration of antiepileptic therapy after the end of electrographic and clinical seizures in ESES.

There is also a very counterintuitive potential alternative approach. For children who have developed reasonable function and are at risk of severe regression from their epilepsy, it might be possible to prematurely terminate the critical period. The goal would be to lock in the functional abilities the child has by preventing the abnormal electrical activity from degrading the thalamocortical architecture. Trazadone, for example, has been characterized in animal models to reduce the amount of cortical plasticity that occurs during slow-wave sleep.[68] There are obvious risks with such an approach, including preventing the normal development of other cortical areas unaffected by the abnormal electrical activity and continued abnormal plasticity in the supragranular layers of cortex (which in some species remains highly plastic even after the critical period ends) driven by spike and waves that may still degrade function. Nonetheless, such an approach might allow for better overall quality of life than if the abnormal electrical activity was allowed to drive plasticity through the entire thalamocortical circuit.

Suppressing thalamic burst activity during sleep

Currently most antiepileptic therapy is directed toward suppressing abnormal cortical electrical activity. Although this approach has had some success, an alternative approach might be to target thalamic activity during sleep, especially in cases in which the bulk of thalamic structures remain. If stronger evidence develops for a thalamic etiology of ESES, a reasonable approach might be to attempt selective silencing of thalamic relay nuclei during sleep, mimicking the activity of the TRN. This would let cortical replay and consolidation proceed in the absence of input from the periphery or abnormal thalamocortical bursting. Although one possible approach is to try to reinstate $GABA_A$ and/or $GABA_B$ balance in the thalamus, as suggested by Guzzetta et al.,[44] an alternative approach, wholly speculative, might be to block T-type calcium channels within the thalamus.[69] Suppressing T-type calcium channels has had some success in experimental models of absence seizures, which, such as ESES, are characterized by rhythmic spike-and-wave activity in the thalamocortical circuit.

Future directions

One limitation of research into ESES is the lack of a good animal model. The studies described above suggest that the developing cat might be an appropriate animal model for these epileptic syndromes. The work by Steriade and Contreras[45] describing continuous spike-wave activity as a result of thalamic injury was performed in cat, as was the work revealing the importance of slow-wave sleep to the development of cortical organization. Unlike the mouse, the thalamic structures of the cat are large enough to allow local ablation of TRN or relay nuclei, and the cortex is highly organized and, at least visual cortex, has been well characterized throughout the developmental critical period. Unlike the case for nonmammalian species,[70] cat brain anatomy is quite analogous to human brain anatomy, and so lessons from cat could be directly applicable to humans. Although the connectivity has been worked out between thalamic relay nuclei and the TRN only in the mouse,[57] the underlying connectivity among thalamic relay nuclei, TRN, and cortical areas are almost certainly similar in the mouse, cat, and human, and should be easily mappable in the cat with optical techniques.[57,71] The ability to test causality and therapies in an animal system could allow for eventual improvement in clinical outcomes.

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